Developmental Origins of Health and Disease (DOHaD) Hypothesis

Subjects: Medicine, General & Internal | Pediatrics

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disease origin development developmental programming

1. Introduction

The “developmental origins of health and disease” (DOHaD) hypothesis refers to the influence of early developmental exposures and fetal growth on the risk of chronic diseases in later periods. Cell differentiation and tissue formation occur in fetal and early postnatal life under the influence of several factors. It is increasingly recognized that perinatal period is of paramount importance for the development and the prevention of subsequent diseases. Neonatologists and pediatricians have an important “window of opportunity” to prevent and cure several diseases and, importantly, promote adult health.

2. Developmental Programming of Diseases and Relative Mechanisms

Critical perinatal factors influencing organogenesis and predisposition to disease include genetic factors, interaction between genes and environment, duration of gestation, and maternal–fetal interactions.

The interaction between genes and the environment in prenatal and early postnatal periods appears to be critical for the onset of diseases in adulthood and has the potential to be modified by interventions. Important factors influencing this interaction include regulation of gene expression and changes in microbiota (individual microorganisms) and microbiome (their collective genomes) [1]. Across perinatal periods, multiple epigenetic mechanisms regulate gene expression without exerting modifications in the DNA sequence: examples are DNA methylation, histone modifications, chromatin remodeling, and transmission of small non-coding RNA. Maternal and paternal contributions to inheritance by means of epigenetic changes in response to nutritional factors and exposure to environmental agents (i.e., drugs, radiations) have recently been reported [2].

Premature birth and intrauterine growth restriction (IUGR) are other important factors considered by the the DOHaD hypothesis. Preterm birth is associated with impaired or arrested structural or functional development of key organs/systems, making preterm infants vulnerable to several diseases at adulthood [3].

Another implication of preterm birth is the lack of hormonal supply with steroid hormones (estradiol and progesterone), which is typically observed among term infants. Both hormones increase up to 100-fold during pregnancy in the mother and the fetus. After preterm birth, these hormones drop dramatically in the mother and the newborn within hours. This is a physiological event at term, but the very preterm infant is disrupted from this huge hormonal supply at a much earlier developmental stage. Preliminary clinical data showed that the replacement of estradiol and progesterone in very preterm infants may improve lung development and neurological outcome [4][5].

Growth restriction, defined as impaired fetal growth compared to expected biological potential in utero, is an additional negative factor increasing the risk of subsequent diseases [6]. Fetal growth is determined by a complex interplay between genetic factors, nutrient and oxygen availability from the placenta, environmental factors, and endocrine modulation of these interactions [6].

True IUGR, compared to constitutional smallness, is a pathological condition in which the placenta fails to deliver an adequate supply of oxygen and nutrients to the developing fetus [7]. Differential expression of growth factors, proteins, and mRNA in placentas of women who delivered growth-restricted fetuses have been reported, suggesting the activation of compensatory mechanisms aimed at maximizing fetal growth [8].

Infants with IUGR, compared appropriately grown gestational age infants, have a significantly higher risk of mortality and neonatal complications with long-term consequences [9][10][11]. The etiology of these complications is due to fetal chronic hypoxia and nutrient deprivation due to placental dysfunction, with impaired fetal hemodynamic adaptations and subsequently altered organ structure and function [12]. For the prevention of IUGR, there is evidence that aspirin modestly reduces small-for-gestational-age (SGA) pregnancy in women at high risk and that a dose of ≥100 mg should be recommended and start at or before 16 weeks of gestation [13]. However, the optimal strategy to identify women who may benefit from prophylactic aspirin still has to be determined.

Changes in microbial population and their interactions with genes and the environment in different organs (i.e., intestine, lungs) have been linked to the development of several diseases, including metabolic syndrome, cardiovascular diseases, and respiratory and psychiatric disorders [1][14].

Suboptimal nutrition and extrauterine growth restriction also increase the risk of complications of prematurity [15]. However, excessive catch-up growth may have negative effects on lifespan [16]. Epigenetic alterations, altered insulin sensitivity, and antioxidant capacity resulting in tissue remodeling and telomere shortening seem to play a significant role in these complications [17][18].

3. Potential Preventive Measures, Interventions and Future Directions

Several preventive measures can be identified and considered to promote long-term health. Examples of useful antenatal measures are: improved identification of subjects with increased risk of complications (i.e., earlier/more frequent ecographic growth assessment), dietary modifications during pregnancy to ensure

normalization of body weight, zinc and iron levels, glycemia and blood pressure control, lifestyle measures (i.e., avoidance of alcohol and tobacco, maximization of maternal education), reduced stress and exposure to pollution), and management of chronic diseases. Some of these measures are currently being evaluated in the context of clinical studies [19][20][21][22][23][24][25][26][27].

The prevention of preterm birth and enhanced maturation (optimal antenatal steroid administration) is of paramount importance. Global policies to enhance health, particularly in low-income countries have been advocated [28]. Specific dietary interventions, including the supplementation of folic acid, zinc, long-chain polyunsaturated fatty acids, and vitamin D, which are possibly associated with favorable epigenetic changes, are under assessment [14].

Finally, the administration of drugs during high-risk pregnancies (i.e., when IUGR is demonstrated) is another potential measure: sildenafil has been investigated but increased fetal death in a clinical trial has led to discontinuation of the study [29]; vascular endothelial growth factor is currently under investigation to promote angiogenesis [30], insulin-like growth factor 1 (IGF-1), antioxidants and melatonin have been tested in preclinical studies [31][32][33]. The identification of the optimal timing of delivery in pathologic conditions (such as IUGR) is another important aspect, and studies are underway in this regard [34].

Postnatal interventions in the early phases of life include promotion of breastfeeding, optimization of nutrition and growth (potentially with administration of hormones/growth factors such as IGF-1 analogues, cautious use and therapeutic drug monitoring of toxic drugs (i.e., nephrotoxic antibiotics, systemic steroids with potential heart and brain toxicity), adequate follow-up of patients at high risk, appropriate resource allocation [28]. The change of maternal and offspring microbiota by dietary modifications (i.e., dietary supplementation with docosahexaenoic acid and arachidonic acid to improve neurodevelopmental outcomes) [22], pre-probiotics, and possibly other factors is a potential intervention needing further studies.

Novel drugs under investigation include lactoferrin and stem cell administration [35][36].

Knowledge translation, the process of putting knowledge into action, is of paramount importance to ensure the use of research findings in decision-making [37]. In fact, the prevention of preterm birth, IUGR, and their long-term complications, as here discussed, is highly relevant for individual and public health. One approach could be to analyze and compare strengths and characteristics of different health systems to inform clinical decision-making, research, and healthcare policy, as recently performed by Japanese and Canadian researchers regarding the prevention and management of preterm birth [38].

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